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INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

IRB Study # 05-2019 (05-EPA-525)
Consent Form Version Date: August 28, 2008
Title of Study: Respiratory effects of short-term low-level chlorine gas exposure

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Funding Source: United States Environmental Protection Agency

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What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

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What is the purpose of this study?

The purpose of this research study is to learn about the effects of short-term, low-level chlorine gas exposure in healthy adults. To do this, we will expose volunteers to an atmosphere containing 0.4 ppm chlorine gas and evaluate changes in lung function and evidence of respiratory tract inflammation. This level of chlorine gas exposure is within workday limits recommended by the United States Occupational Safety and Health Administration, the National Institute of Occupational Safety and Health, and the American Conference of Governmental Industrial Hygienists. You are being asked to be in the study because you are a healthy adult between the ages of 18-35 years.

Are there any reasons you should not be in this study?

You should not participate in this study if you:

1. have problems with excessive bleeding after minor cuts or abrasions.
2. smoked a cigarette in the past 6 months or more than 1 pack-year total.
3. are a competitive swimmer
4. have any current or past history of asthma, or other chronic respiratory condition.
5. have had active allergic rhinitis (hay fever) in the past 3 months
6. have any significant risk factors for cardiovascular disease or anticipate problems with performing moderate treadmill exercise.
7. have ocular disease or symptoms of dry eyes.
8. are pregnant, planning upon becoming pregnant, or breast-feeding.

The physician and medical staff will explain other exclusionary condition in detail to you. In addition, during your participation in this study, you will be asked to refrain from, limit, or control taking the following medications:

*Vitamins C and E.

*Aspirin or similar medication on a regular basis or during the week of testing.

*Use of pool or hot tub the week prior to exposures.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately twenty-five 18-35 year old healthy adult study participants.

How long will your part in this study last?

Your participation in this study will last for approximately 8 to 9 weeks and you will need to visit our facility on 5 or 6 occasions. Each of these visits will last from 2 to 9 hours.

What will happen if you take part in the study?

During the course of this study, the following will occur:

Before you agree to participate in this study, you must read the consent form in its entirety. The research and medical staff will then answer all of your questions and explain all of the risks involved in this study to your satisfaction. Upon deciding to participate in the study and signing the informed consent, you will undergo a training session which, including the informed consent process, takes about 4 hours to complete.

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As was done today, each time you come to the laboratory, your health status will be ascertained by medical personnel (pulse, blood pressure, evaluation of respiratory symptoms and general health) and testing may be postponed for medical reasons. (WOMEN ONLY) On the training day, the two exposure days and the final follow-up day, you will be asked to provide a urine sample so that a urine pregnancy test may be performed. The purpose of this test is to provide evidence that you are not pregnant at the time of the study. The nurse will also ask you when your most recent menstrual cycle began. The results of the pregnancy test will be held in strict confidence. A positive pregnancy test will preclude further participation.

During the training session, you will learn how to perform tests and procedures, which will be expected of you during the experiment. These tests/procedures include measurement of nasal and lung production of nitric oxide, collection of exhaled breath for condensate, performance of nasal resistance measurement and nasal lavage, as well as performance of a series of breathing tests. The lung function tests include evaluating your reaction to an inhaled drug (methacholine) which causes the airways in your lungs to become temporarily narrower. During the training session, you will also receive instruction and training in walking on the treadmill. To qualify for the study, the tests and procedures must show that airflow in your lungs is not obstructed and that your airways are not hyperreactive to the inhaled methacholine.

You will return to the laboratory the day of your first exposure. We will call you a few days before the exposure session to remind you of your scheduled visit. We will also remind you to refrain from alcohol, excessive amounts of caffeine, and from any activities where you could be exposed to high levels of pollutants (e.g. cigarette smoke, paint fumes) the day before your visit. After the health status evaluation and pregnancy check (women only), medical personnel will attach electrocardiograph (ECG) leads to your chest, obtain a blood sample (less than 3 fluid ounces) and ask you to brush your teeth. You will then perform a nasal resistance test and nasal lavage, undergo measurement of nasal and pulmonary NO (nitric oxide) production, perform the exhaled breath collection, perform lung function tests, and complete a symptom questionnaire. It is also possible that you will not perform all the tests described in this consent form. Most of the tests and procedures are considered essential to the study and will be conducted as described in the following text. The tests of exhaled breath analysis, nasal resistance, nasal lavage, and some of the breathing tests (plethysmography, nitrogen washout, and diffusing capacity) are considered secondary and will be performed at the discretion of the investigators based upon the availability and operational status of study personnel and equipment as well as time constraints.

After these pre-exposure tests, you will enter the exposure chamber (approximately 10 x 10 x 13 feet in size) and be exposed for 4 hours to either clean air or air containing 0.4 ppm (parts per million) chlorine gas. While in the exposure chamber, you will alternate 20 minutes of rest with 20 minutes of moderate treadmill walking; this pattern will be repeated throughout your 4 hour exposure. After each exercise period you will complete a symptom questionnaire, perform the nasal resistance test, and perform a lung function test (spirometry).

Following the exposure, you will repeat all of the pre-exposure tests and procedures and a sample of your blood (less than 3 fluid ounces) will be drawn; you will rest in the laboratory or medical station between times of testing. About 90 minutes after the exposure is completed, you will undergo bronchial challenge with inhaled methacholine. You will then be evaluated at the medical station, given instructions for undergoing bronchoscopy, and discharged from the laboratory.

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It is very important that you take nothing by mouth (including water) after midnight. For your own safety, if you take anything by mouth after midnight, you will not be allowed to participate in the bronchoscopy the next day.

You will return to the EPA facility the day after exposure for follow-up testing and bronchoscopy with bronchoalveolar lavage. Your health status will again be ascertained by medical personnel. The follow-up tests are venipuncture and the same tests and procedures you performed prior to the exposure. You will then undergo bronchoscopy; a fiberoptic scope will be inserted through your nose into one of your airways where small areas of your lungs will be washed with sterile saline and a sample of airway lining cells will be obtained with a special brush device.

A minimum of four weeks later you will return to the laboratory to undergo the second exposure and associated testing as described above. On the next day, you will return to the laboratory for follow-up testing and the bronchoscopy.

Study participants who show increased bronchial reactivity to methacholine following the second exposure will return to the laboratory approximately 3 weeks later to verify that there are no long term effects of the chlorine exposure by repeating the spirometry lung function test and performing a bronchial inhalation challenge with methacholine.

At the start-up of the study, 2 to 4 volunteers will be asked complete a "dry run"; the purpose of this dry run is for training of study staff and identifying any time-management problems. This involves a chamber exposure to clean air and the associated pre/post testing except for the venipuncture and next day bronchoscopy. Volunteers who perform the dry run may also participate in the actual study.

Procedures used in this study are described in more detail as follows:

Telemetry

During all activities at the EPA facility you will wear adhesive electrode disks which will be used to provide the investigators with a heart tracing (electrocardiogram); this is primarily a safety precaution.

Nasal Resistance Measurement

This is a non-invasive test. You will apply a nosepiece to your nasal passage for about 5 seconds. Three to five measurements will be made for each nostril.

Nasal Lavage

After observing a demonstration of the delivery technique, you will spray a total of 4 milliliters of saline (less than a teaspoon) into each nostril using a hand held nebulizer that delivers 100 microliter/actuation (spray). Each lavage consists of eight sets of five sprays; you will blow your nose into a specimen cup immediately after each set of five sprays. The entire procedure should be completed in approximately 10 minutes.

Venipuncture

The medical station staff will draw less than 3 fluid ounces of blood before exposure, immediately after exposure and 18 hours after the exposure. The blood samples we collect will be analyzed in the laboratory to measure markers of oxidative stress, antioxidant levels, and proteins involved with iron transport and metabolism, inflammation, and blood clotting. We will also be storing your some of your blood to that we might analyze it in the future for proteins that have yet to be discovered.

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Exhaled breath condensate

At normal breathing frequency and volume, you will breathe air in through your nose and exhale your breath out through your mouth into a wide plastic tubing submerged in ice water. A collection period of up to 15 minutes will be used and generally yield about 2-3 cc of fluid.

Nitric Oxide (NO) Measurement (nasal and lung)

To measure NO nasal production we will ask you to insert a semi-soft probe connected to a sampling line into one of your nostrils. For measurement of lung NO production, you will be asked to breath through a mouthpiece into a sampling bag against exhalation resistance. The entire procedure will be repeated 2-3 times for each nostril and bag sampling; it should be completed in less than 10 minutes. Depending on the analyzer used, we may substitute a direct measurement of nitric oxide during quiet breathing for the bag sampling.

Lung Function Tests

These tests are routine clinical tests. They consist of breathing through a tube attached to a measuring device or breathing in a specialized manner (panting) while seated in an enclosed box called a plethysmograph. During these tests you will be asked to take several full breaths of 100% oxygen and to inhale several breaths containing small quantities of carbon monoxide (0.3%), methane (0.3%), and acetylene (0.3%).

Methacholine Challenge

During your training session, after both exposures, and on the follow-up day you will undergo a test of your airway reactivity to methacholine. This drug causes airway narrowing and testing airway methacholine reactivity is used in evaluating asthma. The test involves inhaling an aerosol containing increasing concentrations of the methacholine alternating with measurements of your lung function. The sequence of aerosol inhalation followed by lung function testing will be repeated until you have a certain amount of airway narrowing. You may perceive this airway narrowing as chest tightness and may wheeze. The effect of this drug should wear off within 30-60 minutes and is quickly reversed by using a standard asthma inhaler. This test will take one to 2 hrs to perform.

Chamber Exposure

You will undergo 2 chamber exposures of 4 hours duration, once to clean air and once to conditioned air with 0.4 ppm chlorine gas. The amount of chlorine gas you will be exposed to is within limits recommended for daily occupational exposures. The chamber conditions are closely monitored and you will be required to exit the chamber if the chlorine level exceeds 0.5 ppm. The order of exposure is randomized and neither you nor the investigator will be informed of the exposure condition. During the exposures, you will perform intermittent (20 minutes on, 20 minutes off) moderate treadmill exercise. You will be requested to breathe through a mouthpiece for 3 minutes during each exercise period to provide a measurement of minute ventilation; your oxygen saturation and heart rate and rhythm will be monitored. Following each exercise session, you will perform a breathing test and the test of nasal resistance. A study investigator will be seated outside the chamber to observe you at all times and will maintain verbal communication. If it appears you are experiencing significant breathing problems, or you develop any symptoms of discomfort (e.g. severe headache, nausea, vomiting, fever) the exposure will be stopped immediately. You may choose to stop the exposure at any time for any reason.

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Bronchoalveolar Lavage (BAL) and Brush Biopsy

Bronchoscopy is frequently used in the diagnosis of lung disease in both adult and pediatric patients. The procedure has also been used in numerous research studies of persons with respiratory disease and in healthy volunteers. The procedure has been used safely many times in studies conducted at our laboratory. The purpose of the BAL procedure is to obtain fluids and cells from the lower regions of the respiratory tract, i.e., the trachea, bronchi and smaller airways. These materials will be analyzed to obtain information about the role of various chemical substances and cells in the pulmonary response to inhaled chlorine gas The bronchoscope is a highly flexible fiberoptic tube that is two feet long and about 1 centimeter in diameter (about the diameter of a pencil). It is an optical device with a light at the end which can be used to transmit images to a camera connected at the other end. Using the bronchoscope, the physician can see into your airways and direct the placement of the bronchoscope. A small channel allows fluid to pass through the bronchoscope.

The BAL procedure will be performed at the laboratory medical station by trained experienced pulmonary physicians. You will be expected at the medical station at 8:00 on the morning after the exposure. If you have had anything to drink or eat since midnight the night before the bronchoscopy you will not be allowed to proceed. You may terminate the bronchoscopy procedure at any time. If the physician deems that you are too uncomfortable or anxious, the procedure will be terminated.

A saline lock will be placed in a vein in your arm (a saline lock is a small catheter that stays in your arm for a short time) and will remain in place so that it can be used to administer medications in case there are any problems during the procedure. You will also be connected to a telemetry monitor that will display heart rate and rhythm, a blood pressure cuff will be placed on your arm, and an oximeter sensor (small band like device) will be placed on a finger to allow the medical staff to monitor you during the procedure. No sedatives and/or narcotics will be administered at any time during bronchoscopy. Atropine may be used at the discretion of the physician; this medication is used to suppress airway secretions and to prevent low heart rate.

Before proceeding, the medical staff will again make certain that you have had nothing to eat or drink since midnight the previous night. They will then give you a lidocaine solution and ask you to gargle with it for a few seconds to anesthetize your throat. You will then be asked to inhale (snort) a small amount of lidocaine jelly through one nostril to anesthetize your nose and the back of your throat. A Q-tip with lidocaine jelly will be gently inserted into your nose to ensure that your nose is completely numb before the bronchoscope is inserted. The procedure will not begin until your nose and throat are well anesthetized. If this cannot be accomplished, the bronchoscopy will not be performed. A tube delivering oxygen will be placed inside your other nostril. Delivery of supplemental oxygen is done as a precaution during all bronchoscopies conducted at our facility.

To start the procedure, the physician will pass the bronchoscope through your anesthetized nasal passage to the back of your throat and then to above your vocal cords. He will then inject a lidocaine solution to numb your vocal cords before passing the bronchoscope into your trachea (windpipe). More lidocaine, up to a safe maximum dose is injected at various points in your trachea and airways to minimize coughing during the procedure. You will experience some cough during the procedure. This is a normal reflex caused by the presence of the bronchoscope in your airway. The bronchoscope will be gently wedged in an airway in the right lung and sterile saline will be injected in your lung through a channel in the bronchoscope. The saline will

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then be gently suctioned from your lung through the channel in the bronchoscope. This sequence will constitute a wash. Six (6) washes will be performed. A total of 270 cc (about one-half pint) of sterile saline will be used during the BAL procedure. Approximately 75% of the saline injected into your lungs will be recovered by aspiration (suction) through the bronchoscope. The remaining 25% (75 cc) is expected to remain in your lungs. The saline left in your lungs should not cause any difficulty breathing or harm you and will be completely absorbed by your lungs within 48 hours.

After the BAL is performed, brush biopsies of your airway epithelium will be taken. A very small brush will be inserted through the channel in the bronchoscope. The brush is visible to the physician performing the procedure through the bronchoscope. Small amounts of surface cells are scraped from the airway by gently brushing the airway several times. Two (2) brush biopsies are taken at one site in the left. After the brush biopsies are obtained, the procedure will be complete and the bronchoscope will be removed from your airway. The total time the bronchoscope will reside in your airways will be 10-20 minutes.

After the procedure the oxygen cannula will be removed if your oxygen saturation is acceptable. Similarly, the chest electrodes will be removed if your heart rhythm is normal. The nurses will check your vital sign immediately after the procedure and one half hour, one hour, and 1.5 hours thereafter. During this time you will sit in a recliner at the medical station for an observation period of an hour. You will not have any food or drink during this time. After the recovery period, the nurses will check your gag reflex. Since the gag reflex will be absent due to anesthesia during the procedure, you will not be allowed to eat or drink until the anesthesia wears off. This normally takes about one to one-and-one half hours. Once your gag reflex returns, you will then be given some juice to sip and then some crackers.

The physician who performed the procedure will check you after the recovery period. You will be discharged if your vital signs are stable and chest examination is normal. Prior to discharge you will be requested to take 600mgm of ibuprofen by mouth; administration of ibuprofen/motrin almost always prevents the post-bronchoscopy malaise and low grade fever that would otherwise occur in about 25% of persons undergoing the procedure (acetaminophen/tylenol is a less effective alternative medication).

If you do not feel like walking, riding your bicycle, driving or taking the bus, the nurses will arrange to have a taxi take you home. The fare will be paid by the laboratory. Before going home, you will be give the phone number of the medical station (966-6232) and pager number to the physician who performed the bronchoscopy with instructions to call if you experience any adverse symptoms such as: 1) persistent fever or fever above 101 degrees Fahrenheit, 2) persistent cough, 3) sputum (phlegm) production, 4) chest pain, 5) coughing up any amount of blood, 6) nose bleeds, or 7) shortness of breath.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study, although you will receive a medical examination that includes blood work, lung function testing, and baseline ECG at no charge. However, this is not a substitute for a routine doctor visit. A member of the medical staff will explain to you any remarkable findings regarding your overall health status. The primary benefit to society produced by this study will be a better understanding of whether or how, exposure to low level chlorine gas affects people. Chlorine gas is identified as an air toxic by the U.S. Environmental Protection Agency and is regulated under the Hazardous Air Pollutants (HAPS) section of the

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Clean Air Act. The results of this study may ultimately play a role in regulation or standard setting for occupational or environmental exposure to chlorine and other respiratory irritants.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you:

If you have any tendency to become uncomfortable in **small closed spaces**, it is possible that you may become uncomfortable during this study. You will be shown the exposure chamber and testing facilities when you are first evaluated for suitability for the study so you may judge whether there is a potential problem.

During one of your exposure sessions you will be **exposed to chlorine gas**. At low levels of exposure, chlorine is a respiratory irritant and it is likely that you will experience mild symptoms of eye, nose and throat irritation, cough and possibly shortness of breath. Such symptoms will likely go away within 2 to 4 hours of your exposure, but may last longer if you are unusually sensitive. After the chlorine exposure, you will likely show small decrements in lung function which will begin to improve on cessation of the exposure and should be completely resolved within 24-48 hours. Following the chlorine gas exposure, your airways may be more sensitive to the inhaled methacholine. Chlorine gas exposure may also temporarily injure the lining cells of your airways, especially in the nose; such effects are not thought to have long-term health consequences.

Performing treadmill exercise may result in muscle soreness or fatigue; such effects are temporary and not harmful. It is possible, that due to an unknown cardiac condition that disturbances in heart function or rhythm could occur; this is considered highly unlikely. It is also possibly that you could injure yourself by falling off the treadmill; you will be trained in treadmill walking to minimize this risk.

There are minimal risks associated with the **lung function measurement**. One of the lung function tests requires that you inhale a gas mixture containing 0.3% carbon monoxide, 0.3% methane, and 0.3% acetylene. Inhalation of high concentrations of carbon monoxide over several minutes may cause headache, nausea, and dizziness. Methane is an inert gas and has small effects at high concentrations. Acetylene is a gas that at high concentrations may cause headache and dizziness. However, the concentrations of the gas mixture you will inhale are very low, you will inhale them for only a very short time and they should not cause any symptoms. Inhaling the **methacholine** aerosol will cause constriction of the airways (breathing tubes) within your lungs. This may cause a feeling of "tightness" within your chest. This feeling usually disappears within 30 to 60 minutes and, if necessary may be treated with an asthma inhaler medication (albuterol; "Ventolin or Proventil") which will open the airways. There are no systemic effects of methacholine.

Venipuncture risks include the possibilities of fainting, bruising, or infection, although these are unlikely and are minimized by performance of venipuncture by trained personnel.

There are minimal risks associated with monitoring your heart by telemetry. Preparing your skin for **placement of ECG electrodes** and removing the electrodes at the end of the day may cause some irritation, itching, or burning in some people. If this occurs you should inform the nursing staff.

There are essentially no risks to performing the exhaled breath collection, nasal lavage, nasal resistance measurements, or nasal and pulmonary NO production evaluations.

There are several risks associated with performing **bronchoscopy,** although these risks are exceedingly small when bronchoscopy is performed on young healthy subjects, the type of

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people involved in this study. The primary risk of bronchoscopy is discomfort in the nose and throat, which is caused by having the bronchoscope inserted through the nose and passed through the back of your throat to reach the trachea (windpipe) and the airways leading to the lungs. This discomfort is alleviated with topical lidocaine, which you will gargle and inhale prior to the procedure. If you are suffering from discomfort in your nose and throat because they are not adequately anesthetized, you can request that more lidocaine be used, however, there is a limit to the maximum amount of lidocaine that can be given. If you are unable to tolerate the passage of the bronchoscope thorough your nose and throat because of pain in spite of having received the maximum allowable amount of lidocaine, the procedure will be immediately terminated .

A second risk of having bronchoscopy performed is coughing. Coughing is caused by irritation from the bronchoscope itself or the instruments used to obtain the biopsy material. Lidocaine liquid can be sprayed into your airways thorough the bronchoscope to relieve coughing. If the coughing is uncontrollable even with the use of the maximum amount of lidocaine, the procedure will be stopped immediately.

Lower airway bleeding can also occur from injury to the airway wall caused by the bronchoscope or the biopsy procedures. This bleeding is usually very minor (less than a teaspoon of blood). The bleeding resolves spontaneously within several minutes. If the bleeding is mild to moderate, epinephrine (adrenalin) can be sprayed on the bleeding site through the bronchoscope to hasten the clotting.

The **lidocaine** used for anesthesia during the procedure can have some adverse effects because some of the lidocaine can be absorbed into the blood stream from the nose and lungs. If you are allergic to lidocaine, you could develop itching, hives, difficulty breathing, and possibly shock (a dangerous drop in blood pressure). This risk is minimal, but you will be excluded from participating in this study if you are allergic to lidocaine or any other topical anesthetic that is commonly used in minor surgical or dental procedures. Lidocaine can also cause symptoms in your central nervous system (confusion, tremor, euphoria, or, rarely, seizures) or heart rate disturbances (very fast or very slow heart rate) if an excessive dose of medication is used. Finally, a death in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during bronchoscopy has been reported from Rochester, New York. However, no serious side effects of this medication have been noted at lower doses such as those described in this protocol which uses up to 360 milligrams of lidocaine during the entire procedure. If any problems develop secondary to the use of lidocaine, the physician bronchoscopist and the doctor on duty that day at the Human Studies Division of the EPA will be available to handle these problems.

Atropine, the medication that may be given to you by vein before the procedure starts, is given to help prevent your blood pressure and pulse from falling when the bronchoscope is first put into your airway, and to reduce the amount of secretions present in your nose, throat, and airways during the procedure. Atropine can cause you to have a dry mouth and nose as well as an increased pulse for about 30 to 60 minutes after it is given. These side effects are not harmful to you, and they wear off within 30 to 60 minutes after the drug is given.

The **placement of an IV catheter** in your arm can cause some pain. However, the IV is placed by a registered nurse who is very experienced in this technique, and the pain is very minor, usually resolving very soon after the IV catheter is in place. Rarely, placement of an IV catheter can result in the formation of a hematoma (bruise) at the site of the IV after it is removed. Also, a rare complication of IV placement is skin infection or an infection of the vein in which the IV catheter has been placed. The risk of getting an infection from the IV are minimized by the nurse's use of sterile technique of place the catheter. If you do have signs of

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infection at the IV site (redness, warmth, painful skin, swelling) after completion of the procedure, you will need to contact the EPA medical station (966-6232) or the physician who performed the bronchoscopy. You are not at increased risk by having blood drawn through the IV catheter.

Some subjects who undergo bronchoscopy have a low-grade fever (less than 101 degrees Fahrenheit) and experience symptoms of malaise and low energy after the procedure is completed. To prevent this from occurring you will be asked to take 600 mgm of ibuprofen (advil, motrin) before you are discharged from the medical station. This fever is almost always benign, occurs in approximately 25 percent of all subjects who undergo bronchoscopy, and is almost always prevented with the use of ibuprofen. Nevertheless, a persistent fever or any temperature of greater than 101 degrees Fahrenheit might mean that you have an infection, particularly pneumonia. Therefore, if you have any fever greater than 101 degrees Fahrenheit after the bronchoscopy or a fever that doesn't resolve in 24 hours after the procedure is completed, you should contact the EPA medical station or the physician who performed the bronchoscopy so that arrangements can be made for you to be examined by one of the physicians at EPA. You will be called 24 hours after the procedure to check on your condition. In addition, there may be uncommon or previously unrecognized risks that might occur. You should report any problems to the researchers.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

. The first participant in this study was exposed to 0.5 ppm chlorine exposure for 4 hours. This individual reported mild symptoms, showed the expected small decrement in pulmonary function, but incurred a larger than expected increase in methachloline sensitivity. We then reduced the exposure concentration to 0.3 ppm chlorine and modified the exercise protocol. Since the reduction in exposure level, two individuals have undergone exposure for 4 hours to 0.3 ppm chlorine. They both reported mild symptoms, showed no change in pulmonary function, and showed no change in response to methacholine challenge. We have since again amended the protocol to increase the chlorine exposure level from 0.3 ppm to 0.4 ppm. Of note, the subject exposed to 0.5ppm chlorine has returned for her clean air exposure and her methacholine sensitivity has returned to the level observed during her training session.

How will your privacy be protected?

You will be assigned a study identification number. Names of subjects associated with ID numbers will be archived and locked; only medical and scientific personnel associated with this study will have access to this information. No personal identifying information will be attached and/or recorded in the data log sheets, biologic samples, or electronic data sets. No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, the U.S. Environmental Protection Agency and UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

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Study samples will be stored in a secure room with restricted access. The sample will be prepared and stored indefinitely in a freezer for future testing. Portions of the samples may be shared with researchers at other scientific institutions, however, only coded samples will be sent. Under no circumstances will any identifying information be sent along with samples to outside investigators. All medical records generated during this study will be kept in the medical records office at the EPA Human Studies Facility.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care. If you believe you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving $12.00 per hour for taking part in this study plus additional incentives for preforming procedures which produce discomfort (venipuncture $20, nasal lavage $20, bronchoscopy with BAL $350). You will be paid a bonus of $25 for arriving on-time on the two exposure days. You will be paid the same whether or not the follow-up methacholine challenge is required. You will also be paid a completion bonus of $125 for completing all parts of the study. A detailed break-down of the payment schedule and time requirement is as follows:

Procedure	Time	Payment
Training	4 hr	$ 48
Chamber exposure (9 hr)	18 hr	$ 216
BAL Day Testing (2hr)	4 hr	$ 48
F/U Methacholine Challenge	2 hr	$ 24
6 Venipuncture ($20 each)	N/A	$ 120
7 Nasal lavages ($20 each)	N/A	$ 140
2 bronchoscopies ($350 each)	N/A	$ 700
2 On-time bonuses ($25 each)	N/A	$ 50

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1 Completion bonus ($125)	N/A	$ 125
TOTAL :		$1471

It is expected that if you undergo the training, the two exposures and bronchoscopy days and the follow-up day with the called for venipunctures, and bronchoscopies and qualify for the completion bonus, you will receive a total payment of $1471. If you complete the dry run at the beginning of the study, you will be paid an additional $148. You will be paid a nominal fee to offset transportation expenses if you travel from outside the Chapel-Carrboro area, and parking will be provided. All payment will be made at the end of the study unless a specific request for prior partial payment is made by the subject.

You understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty, and without losing benefits to which you would otherwise be entitled. If you elect to terminate your participation in the study, you will be paid for that portion of the study which has been completed. The investigators also have the right to stop your participation in the study at any time. If you develop an illness or injury that precludes you from further participation in the study you will be paid for the portion of the study you have completed.

Payments totaling more than $600 in a year from a single or multiple EPA studies will be reported to the IRS.

Will it cost you anything to be in this study?

The U.S. EPA will pay the costs of this research. You will not be billed for any procedures.

Who is sponsoring this study?

This research is funded by the United States Environmental Protection Agency. Several of the investigators including the Principal Investigator are federal employees. The researchers do not, however, have a direct financial interest in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

initials:_____

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 and/or the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217 or by email to IRB_subjects@unc.edu.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

initials:_____